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EDITORIAL

Which PET Radiopharmaceutical for Brain Tumors?

After an initial period of skepticism about the meaning and purpose of PET in the study of brain tumors, we are now observing an explosion of interest in the subject. The message that CT and MR examinations, despite their exquisite anatomical depiction, fail to provide the critically important information necessary for appropriate management of these neoplasms, has pierced through. Twelve years ago, our fledgling PET tumoral research at the National Institutes of Health was labeled by some as "redundant and irrelevant." CT and the just-being-introduced MRI were rendering brain tumor diagnosis a "settled matter."

Yet, today the clinical challenge of handling primary brain tumors remains formidable and controversies abound (*1–4*). When should we start to use any of the three main therapeutic means available to us, i.e., surgery, radiotherapy, and chemotherapy? In the low-grade gliomas, should we delay surgery and radiotherapy as long as possible? Is open surgery actually necessary in every case of high-grade glioma? How far can we rely on stereotactic sampling? Should we favor stereotactic radiosurgery for suspected high-grade, deep lesions, even in the absence of histologic confirmation? Do CT, MR, or arteriography allow us to grade primary brain tumors? What path should we follow when confronted with renewed clinical deterioration after radiotherapy, considering that CT, MR, and arteriography do not allow us to confidently differentiate between tumor recurrence and cerebral radiation necrosis? Should we proceed with additional surgery, interstitial radiotherapy, pass to chemotherapy, or abstain from further treatment? Should we obtain histologic confirmation? Should histology represent the definitive guide at every step of the management? Does, in fact, histology consistently assist us in the prognostic assessment of these patients? Or rather, has the static histologic examination exhausted its role, held since the age of Cruveilhier, Rokitansky and Virchow, as the ultimate, unappealable test? The list of questions seems inexhaustible.

What is clearly needed is an assessment of the biologic behavior of the tumor, a complex matter, considering that even the frequency of natural change to higher malignancy of low-grade neoplasms remains controversial (*2,3*). Use of radiotracers, particularly analogs of physiologic compounds, is considered the tool most likely to assist us in this area. Even in 1961, a report dealing with radioisotope brain imaging (*5*) noted that: "The degree of differentiation of a tumoral lesion is important in determining the uptake ratio. Tumors of the glioblastoma group show a high ratio. On the other hand relatively benign and well differentiated tumors, such as some astrocytomas, present the lowest concentration of isotope."

When, in 1979, the seminal contribution by Reivich et al. on PET with ^{18}F-2-deoxyglucose (FDG) was published (*6*), it was only obvious that this tracer, with its capability to measure the degree of cerebral tissue glucose utilization, should be tried for grading brain tumors. The linkage glucose consumption-malignancy had been forcefully proposed by Otto Warburg, who suggested that neoplasms display higher rates of aerobic glycolysis with increasing degree of malignancy (*7*). (By aerobic glycolysis, Warburg meant the metabolism of glucose to lactate rather than to CO_2 and H_2O, even in the presence of adequate available O_2.) Thus, the already high energy demands of rapidly proliferating tumoral tissue are further increased by the shift toward the less efficient glycolytic pathway. This marriage of a proven radiotracer with a compelling theoretcial framework proved successful; PET centers throughout the world now use FDG to study brain tumors, as well as tumors in other parts of the body.

However, studies of neoplasia with PET have not been limited to a single radiopharmaceutical. Besides FDG, other tracers tagged with positron emitters have been suggested, introduced and tested, in mostly smaller and sometimes larger series of patients, to assess the biologic behavior of the tumor. They include other sugars and sugar derivatives, amino acids, nucleosides, putrescine, and receptor ligands labeled with ^{18}F, ^{11}C, or ^{13}N, as well as ^{13}N-labeled ammonia. Appropriate radiopharmaceuticals have also been used in tumors for PET studies of disruption of the blood-brain barrier, changes in blood flow, blood volume, pH, and pharmacokinetics of chemotherapeutic drugs. In this issue of the *Journal*, an ^{18}F-tagged

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amino acid is proposed as a potential brain tumor tracer (*8*). I suspect that the casual, as well as the more deeply involved perusers of the large pertinent literature must be quite confused. The claims of investigators proposing new pharmaceuticals for clinical PET studies of tumors are clamorous and discordant. Unfortunately, some investigators seem to be impressed by tracer features that are not relevant to the critical questions (see above) which a radioisotope procedure should help clarify. In any event, these features include capabilities that are possessed to a larger degree by other neuroradiologic methods—in particular CT and MR scanning. Whether any radiotracer can reveal tumoral infiltration beyond the limits of the lesion outlined by CT or MR, or within edematous areas, remains to be proven.

In 1968, we published "Which radioisotopes for brain scanning?", a thorough review describing all the cerebral scanning radiotracers available at the time and assessing their relative merits (*9*). It is time again to take stock. However, rather than discussing the advantages and disadvantages of the numerous radiopharmaceuticals proposed for tumor PET scanning, I believe it is more constructive, at this time, to outline the "clinical" features required for an "ideal" oncologic PET tracer, as well as some of the technical and interpretative requisites for its optimal utilization. The following comments avoid the formalisms of tracer distribution theories. They derive directly from 40 years of personal experience in brain tumor diagnosis (*10*), including some 1000 PET studies carried out in the last decade.

FEATURES OF THE "IDEAL" PET TRACER FOR BRAIN TUMORS

1. A clear rationale for the choice of a new tracer is desirable, including a theoretical model and experimental data, preferably autoradiographic.

2. The tumoral uptake should be relatively independent of the status of the blood-brain barrier, since breakdown of the blood-brain barrier is not necessarily linked to the tumor nature or clinical behavior.

3. Tracer accumulation within the tumor should persist for a period long enough to allow the "clinical" PET procedure to be carried out. This condition also implies a reasonable half-life of the tagging radioisotope.

4. Irrespective of the responsible mechanism—active transport, irreversible metabolic turnover (metabolic trapping), or receptor binding—*the degree of tumoral uptake should have a clear relationship with the tumor grade.* Tracers which accumulate without a meaningful difference *both* in low- and high-grade tumors are of limited or questionable value.

This statement has several corollaries:

a. In heterogeneous tumors, the tracer should allow distinction of non-viable components (necrotic areas, cysts) from more biologically aggressive neoplastic foci.
b. In post-radiotherapy or post-radiochemotherapy cases, the tracer should differentiate between tumor recurrence (usually consisting of high-grade tumoral tissue) and radiochemonecrosis.
c. Postsurgically, possible neoplastic residua should show a degree of tracer uptake permitting differentiation from postoperative changes.

5. Assessment of tumoral biology should not be limited to the histologic grade. Patient survival time and clinical status are important issues as well. In fact, the tracer capabilities are better appraised on the basis of the patient's destiny, rather than on a categorical reliance on the histologic features, which not infrequently are determined by the pathologist on the basis of subjective criteria (*11*). Particularly important in this regard is the critical, and not infrequently controversial, distinction between Grade II and Grade III [Kernohan classification (*12*)], as well as the distinction between viable tumor and tumor damaged by radiation.

6. The purity of the radiopharmaceutical and the scanner resolution should be adequate. Regarding the latter, the scanner should allow clear distinction of gray structures from white matter. Actually, good scanners provide excellent anatomical display, belying the notion that PET scanning depicts function but not form.

7. Tested quantitative reliability should be available for support in a specific case, as well as for analysis of groups of cases.

8. The area of reference should be chosen on the basis of well-established compartmental (e.g., gray, white matter) distribution of the tracer in question, and on preferential origin and location of the type of tumor under study.

9. A modicum of experience in tumor management and reasonable interpretative skill by the reader of the scans are indispensable. I never fail to be amazed by the lack of appreciation that, in the interpretation of a clinical imaging study such as PET, the diagnostician's capabilities are a key factor, just as the experience and skill of the surgeon are recognized to be of paramount importance in a surgical procedure.

10. Assessment of tracer capabilities should be based on a reasonable number of cases, certainly more than twenty.

I am convinced that a PET radiopharmaceutical which is found to fulfill the above "clinical" requirements, after proper testing, is the tracer of choice for the appraisal and management of patients harboring central nervous system tumors.

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Determining the Value of Diagnostic and Screening Tests

Barbara J. McNeil and S. James Adelstein

Rapid advances in medical technology frequently lead to the development of new diagnostic procedures whose value should be determined before they are used widely. These values can be measured in terms of health and money. Health values relate to the accurate identification and successful treatment of disease; financial values relate to the husbanding of monetary resources expended for health services.

Fundamentals of Decision Making

A number of methods have been used to evaluate diagnostic procedures. The two used most frequently are: the decision matrix and the receiver operating characteristic (ROC) curve.

The Decision Matrix. This relates results of a diagnostic test with a binary outcome (normal, abnormal) to clinical or pathologic findings, also with a binary outcome. Five ratios can be derived from this table and are used to characterize such binary tests:

1. The true-positive (TP) ratio is the proportion of positive tests in all patients with disease—the sensitivity of the test.
2. The false-positive (FP) ratio is the proportion of positive tests in all patients without disease.
3. The true-negative (TN) ratio is the proportion of negative tests in all patients without disease and is the specificity of the test.
4. The false-negative (FN) ratio is the proportion of negative tests in all patients with disease.
5. The likelihood ratio (L) of a test is the ratio of the TP ratio to the FP ratio.

It is important to emphasize that these ratios describe the sensitivity and specificity of the test; they cannot be used alone to determine the significance of a positive or negative test. An extended analysis is required to determine the probability that a patient does or does not have disease, given the test result.

The ROC Curve. When tests do not have binary outcomes, but rather have a continuum of values, the true- and false-positive ratios vary with the value selected as the cutoff point. Routine chemistry examinations and radioimmunoassays are examples of such tests. We can graphically visualize the effect of changes in the cutoff point on test sensitivity by using a ROC curve, a plot of the true-positive ratio against the false-positive ratio for varying cutoff points.

General Considerations

Health Values. Health values associated with diagnostic tests are best understood through a simplified model of the diagnostic and therapeutic process. In this model, a patient with a symptom complex or a syndrome enters the diagnostic process. At the first decision point, a diagnostic test is either performed or not performed. In the former case, the first chance point depicts the results of this test in terms of the amount of information achieved. The test can provide new information (+), no information (0), or misleading information (−). This stage of the diagnostic process provides the first point at which we can measure the value of a diagnostic test and satisfy those who would claim that the ultimate test of a diagnostic procedure is its ability to sort patients with regard to specific diseases.

After diagnostic testing, treatment is instituted and the results of treatment are depicted at the second and final chance point. These outcomes represent a continuum of states, ranging from perfect health (cure) to death. The second point provides the second opportunity for measuring the value of a diagnostic procedure and satisfies more operationally-oriented physicians who claim that the ultimate test of a diagnosis is the extent to which it can save lives, restore health, or alleviate suffering. If the test is not performed, treatment is instituted on the basis of available information with the same continuum of outcomes.

Financial Values. The financial aspects of the diagnostic and therapeutic process can also be considered. In broad terms, the financial value of a test lies in its ability, if truly negative, to eliminate costs associated with unnecessary diagnostic procedures and therapeutic regimens or, if truly positive, to eliminate financial costs caused by the progression of untreated disease. These benefits are difficult to measure directly. Therefore, three other financial measures are frequently used in evaluating diagnostic tests: (a) the total cost of diagnosis and therapy once the test is introduced; (b) the average cost of achieving a given unit of health by use of the test; and (c) the marginal cost of achieving one additional unit of health by one procedure over another.

The elementary principles and the clinical examples reviewed in this article have been presented in order to provide a systematic approach to the measurement of the health and financial values of diagnostic and therapeutic intervention. It is clear that measurement of these values is becoming increasingly important as new and untested procedures and instruments are introduced. Hopefully, with knowledge of these values, the resources allocated for medical care can be optimally utilized. ■